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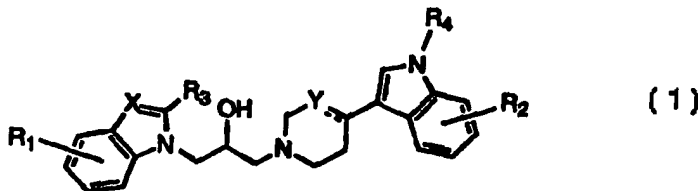
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(54) Title: INDOLYL DERIVATIVES AS SEROTONERGIC AGENTS



(57) Abstract

The present invention provides compounds of formula (1) wherein R₁ and R₂ each independently represent hydrogen, hydroxy, F, Cl, Br, I, CN, 1 to 6 carbon alkyl, 1 to 6 carbon alkoxy, nitro CF₃ and phenyloxy or benzyloxy, in which the aromatic ring can be optionally substituted by from 1 to 3 groups selected from C₁-C₆ alkoxy (preferably OMe), F, Cl, Br, I, and CF₃; R₃ and R₄ are each independently a hydrogen, a 1 to 6 carbon alkyl or a CH₂Ph in which the phenyl ring can be optionally substituted by from 1 to 3 groups selected from C₁-C₆ alkoxy (preferably OMe), F, Cl, Br, I, and CF₃; Y is selected from CH₂ or CH and, X is selected from a group represented by N, CR₃, CHR₃, CHCH₃; or a pharmaceutically acceptable salt thereof, as well as pharmaceutical compositions and methods of using the compounds to treat central nervous system disorders, such as depression, anxiety, drug withdrawal, eating and sexual disorders and other conditions for which serotonin reuptake inhibitors are used.

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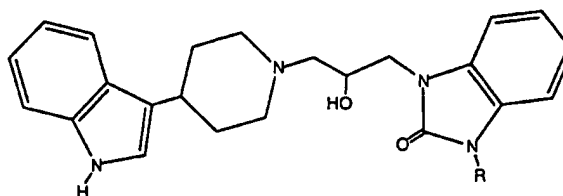
INDOLYL DERIVATIVES AS SEROTONERGIC AGENTS

This application claims the benefit of U.S. Provisional Application No. 60/122,057, which was converted from U.S. Patent Application No. 09/069,045, filed 5 April 29, 1998, pursuant to a petition filed under 37 C.F.R. 1.53(c)(2)(i).

This invention concerns a series of novel heteroaryl- β -hydroxypropylamines which are effective pharmaceuticals for the treatment of conditions related to or are affected by the reuptake of serotonin. The compounds are particularly useful for the 10 treatment of depression, anxiety, drug withdrawal, eating and sexual disorders and other conditions for which serotonin reuptake inhibitors are used.

Background to the Invention

15 In their article "4-(Indolyl-3)-1-(benzimidazolonylalkyl)-piperidines, a Novel Group of Potential Antiallergy Compounds", *Arzneim.-Forsch.*, 35(1), 272-276 (1985), Freter et al. disclose compounds of the formula:



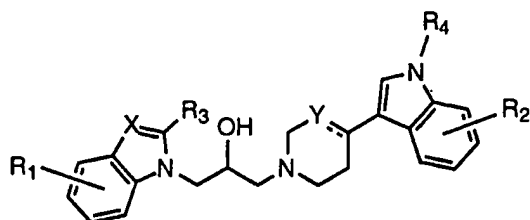
20 as anti-allergy agents by virtue of their histamine H1-blocking actions in addition to weak mast cell stabilizing properties.

Summary of the Invention

25 Depression is a psychiatric condition thought to be associated with decreased serotonin release. Most antidepressant agents (e.g. fluoxetine) potentiate the effects of serotonin by blocking the termination of its activity through reuptake into nerve terminals. The present invention provides a series of novel indolyl derivatives which inhibit the reuptake of serotonin, to processes for their preparation, to pharmaceutical compositions containing them and to their use in therapy for the treatment of central 30 nervous system disorders, particularly depression.

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Compounds of the present invention are represented by the general formula (1)



(1)

5 wherein:

R_1 and R_2 each independently represent hydrogen, hydroxy, F, Cl, Br, I, CN, 1 to 6 carbon alkyl, 1 to 6 carbon alkoxy, nitro, CF_3 and phenyloxy or benzyloxy, in which the aromatic ring can be optionally substituted by from 1 to 3 groups selected from C_1 - C_6 alkoxy (preferably OMe), F, Cl, Br, I, and CF_3 ;

10 R_3 and R_4 are each independently a hydrogen, a 1 to 6 carbon alkyl or a CH_2Ph in which the phenyl ring can be optionally substituted by from 1 to 3 groups selected from C_1 - C_6 alkoxy (preferably OMe), F, Cl, Br, I, and CF_3 ;

Y is selected from CH_2 or CH and,

X is selected from a group represented by N, CR_3 , CHR_3 , CHCH;

15 or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of this invention are those in which X is N and R_1 , R_2 , R_3 , R_4 and Y are as defined above. Another preferred group herein comprises compounds wherein X is CR_3 , CHR_3 or CHCH and R_1 , R_2 , R_3 , R_4 and Y are as defined above.

20

The pharmaceutically acceptable salts are the acid addition salts which can be formed from a compound of the above general formula and a pharmaceutically acceptable inorganic acid such as phosphoric, sulfuric, hydrochloric, hydrobromic, citric, maleic, fumaric, acetic, lactic or methanesulfonic acid.

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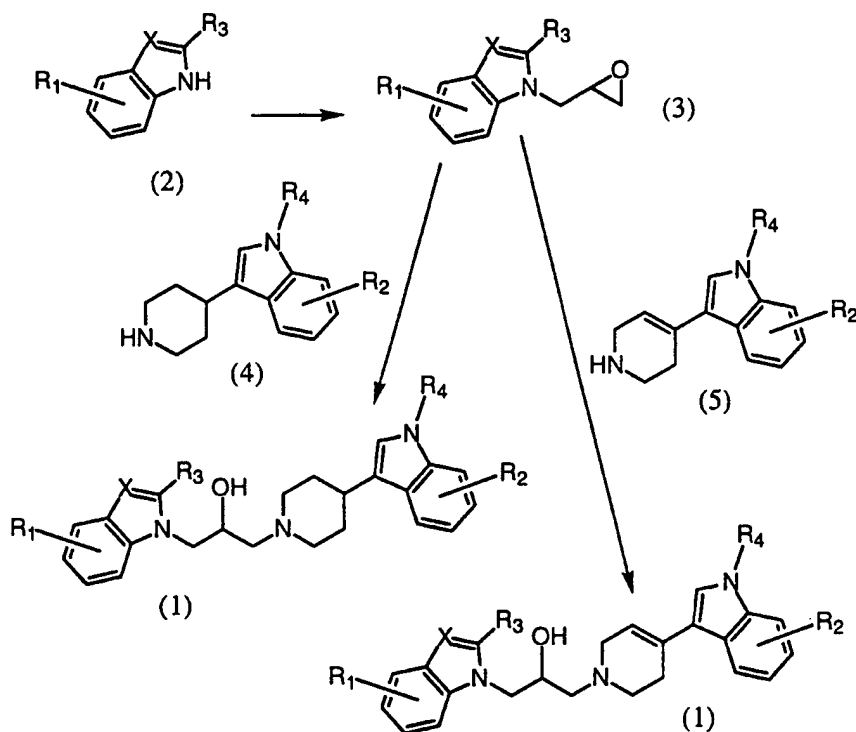
Detailed Description of the Invention

Compounds of the present invention may be prepared using conventional methods. For example, treatment of the indole or benzimidazole derivative (2) with

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glycidyl tosylate affords the epoxide (3). Reaction of the epoxide with the piperidine or tetrahydropyridine derivatives (4) and (5) affords the respective products (1).

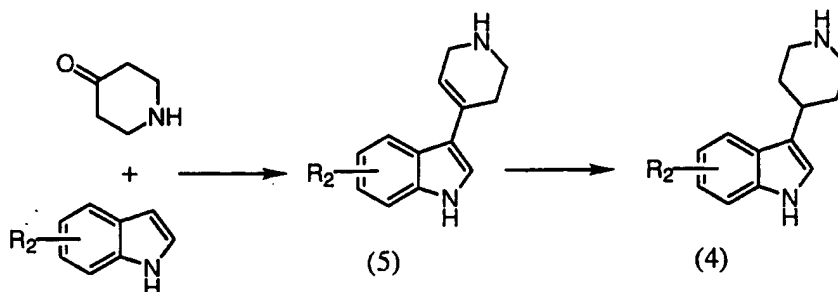


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The preparation of the appropriately substituted 3-(4-piperidinyl)indoles and 3-(4-tetrahydropyridinyl) indoles can be achieved by known and conventional methods. For example, the reaction of an optionally substituted indole with 4-piperidone affords the 3-(4-tetrahydropyridinyl)indole (5). This can be reduced using standard catalytic hydrogenation methodology to afford a 3-(4-piperidinyl)indole (4). Such methodology is described in C. Gueremy et al., *J. Med. Chem.*, 1980, 23, 1306-1310, J-L. Malleron et al., *J. Med. Chem.*, 1993, 36, 1194-1202 and J. Bergman, *J. Heterocyclic. Chem.*, 1970, 1071-1076.

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The present invention provides methods for inhibiting the reuptake of serotonin in mammals, preferably in humans. Compounds of the present invention inhibit with very high affinity the binding of paroxetine to the serotonin transporter, and consequently, they are useful for the treatment of central nervous system disorders such as depression, anxiety, including generalized anxiety disorder, sleep disorders, sexual dysfunction, obsessive-compulsive disorders, obesity, bulimia nervosa, migraine, chronic fatigue syndrome, pain, particularly neuropathic pain, panic disorder, post traumatic stress disorder, late luteal phase dysphoric disorder (also referred to as premenstrual syndrome), Tourette's syndrome, alcohol and cocaine addiction, Parkinson's disease, schizophrenia and for cognition enhancement such as in Alzheimer's disease.

It is understood that the therapeutically effective dosage to be used in the treatment of a specific psychosis must be subjectively determined by the attending physician. Variables involved include the specific psychosis or state of anxiety and the size, age and response pattern of the patient. The novel method of the invention for treating conditions related to or are affected by the reuptake of serotonin comprise administering to warm-blooded animals, including humans, an effective amount of at least one compound of this invention or a non-toxic, pharmaceutically acceptable addition salt thereof. The compounds may be administered orally, rectally, parenterally, or topically to the skin and mucosa. The usual daily dose is depending on the specific compound, method of treatment and condition treated. An effective dose of 0.01 - 1000 mg/Kg may be used for oral application, preferably 0.5 - 500 mg/Kg, and an effective amount of 0.1 - 100 mg/Kg may be used for parenteral application, preferably 0.5 - 50 mg/Kg. The therapeutically effective dosage to be used in the treatment of a specific psychosis must be subjectively determined by the attending

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physician. The variables involved include the specific malady or disorder and the size, age and response pattern of the patient.

The present invention also includes pharmaceutical compositions containing a
5 compound of this invention, or a pharmaceutically acceptable salt thereof, and one or
more pharmaceutically acceptable carriers or excipients. Applicable solid carriers or
excipients can include one or more substances which may also act as flavoring agents,
lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders
or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a
10 finely divided solid which is in admixture with the finely divided active ingredient. In
tablets, the active ingredient is mixed with a carrier having the necessary compression
properties in suitable proportions and compacted in the shape and size desired. The
powders and tablets preferably contain up to 99% of the active ingredient. Suitable
solid carriers include, for example, calcium phosphate, magnesium stearate, talc,
15 sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium
carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange
resins. Liquid carriers may be used in preparing solutions, suspensions, emulsions,
syrops and elixirs. The active ingredient of this invention can be dissolved or
suspended in a pharmaceutically acceptable liquid carrier such as water, an organic
20 solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier
can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers,
buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening
agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples
of liquid carriers for oral and parenteral administration include water (particularly
25 containing additives as above e.g. cellulose derivatives, preferably sodium
carboxymethyl cellulose solution), alcohols (including monohydric alcohols and
polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated
coconut oil and arachis oil). For parenteral administration the carrier can also be an oily
ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in
30 sterile liquid form compositions for parenteral administration. Liquid pharmaceutical
compositions which are sterile solutions or suspensions can be utilized by, for example,
intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be
administered intravenously. Oral administration may be either liquid or solid
composition form.

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Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

The affinity of drugs for the serotonin transporter was determined by assessing the ability of agents to displace specifically bound ³H-paroxetine binding from rat cortical membranes. This procedure is a modification of that used by Cheetham et al., 1993 (Neuropharmacol. 32:737-743, 1993). Nonspecific binding was determined using fluoxetine. Using this assay, the following K_i's were determined for a series of standard serotonin uptake inhibitors.

³H-Paroxetine Binding to Assess Affinity of Drugs for the Serotonin Transporter:

A protocol similar to that used by Cheetham et al. (Neuropharmacol. 32:737, 1993) was used to determine the affinity of compounds for the serotonin transporter. Briefly, frontal cortical membranes prepared from male S.D. rats were incubated with ³H-paroxetine (0.1 nM) for 60 min at 25°C. All tubes also contained either vehicle, test compound (one to eight concentrations), or a saturating concentration of fluoxetine (10 μM) to define specific binding. All reactions are terminated by the addition of ice cold Tris buffer followed by rapid filtration using a Tom Tech filtration device to separate bound from free ³H-paroxetine. Bound radioactivity was quantitated using a Wallac 1205 Beta Plate® counter. Nonlinear regression analysis was used to determine IC₅₀ values which were converted to K_i values using the method of Cheng and Prusoff (Biochem. Pharmacol. 22: 3099, 1973); $K_i = IC_{50} / ((\text{Radioligand conc.}) / (1 + KD))$.

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<u>Compound</u>	<u>Inhibition of [3H]-Paroxetine binding</u>
	<u>Ki (nM)</u>
Clomipramine	0.18
Fluoxetine	4.42
5 Imipramine	17.6
Zimelidine	76.7

The results for a number of examples of compounds of formula (1) in this standard experimental test procedure were as follows:

<u>Compound</u>	<u>Inhibition of [3H]-Paroxetine binding</u>
	<u>Ki (nM)</u>
Example 8	1.4
Example 10	0.01
15 Example 11	0.04
Example 12	1.7
Example 13	0.4
Example 14	0.03
Example 15	0.3

20 The following non-limiting specific examples are included to illustrate the synthetic procedures used for preparing compounds of the formula (1). In these examples, all chemicals and intermediates are either commercially available or can be prepared by standard procedures found in the literature or are known to those skilled in
25 the art of organic synthesis.

Example 1

1-N-Glycidyl-5-fluoro-indole

30 Epibromohydrin (1.4 ml, 16.5 mmole) was added to a stirred solution of 5-fluoroindole (2.0 g, 15 mmole) and sodium hydride (0.66 g, 16.5 mmole) in anhydrous DMF (20 ml), and the mixture was heated at 60°C under nitrogen for 15 hours. Water (100 ml) was added and the product extracted into CH₂Cl₂ (3 x 35 ml). The combined organics were washed with water (25 ml), brine (25 ml) and dried over
35 anhydrous sodium sulfate. Filtration and concentration in vacuo gave the crude product

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as a viscous yellow colored oil (2.7 g). This was purified by flash silica gel chromatography (30% ethyl acetate in hexane) to afford the titled product as a viscous oil (2.5 g, 89% yield).

Elemental Analysis for: C₁₁H₁₀FNO

5 Calculated: C, 69.10; H, 5.27; N, 7.33

Found: C, 69.24; H, 5.67; N, 7.36

Example 2

1-N-Glycidyl-4-methoxy-indole

10

Epibromohydrin (0.64 ml, 7.5 mmole) was added to a stirred solution of 4-methoxyindole (1.0 g, 6.8 mmole) and sodium hydride (0.3 g, 7.8 mmole) in anhydrous DMF (20 ml), and the mixture was heated at 60°C under nitrogen for two hours. Water (100 ml) was added and the product extracted into CH₂Cl₂ (3 x 25 ml).

15 The combined organics were washed with water (25 ml), brine (25 ml) and dried over anhydrous sodium sulfate. Filtration and concentration in vacuo gave the crude product as a yellow colored oil (1.5 g). This was purified by flash silica gel chromatography (30% ethyl acetate in hexane) to afford the titled product as a light oil (1.27 g, 92% yield).

20 Elemental Analysis for: C₁₂H₁₃NO₂

Calculated: C, 70.92; H, 6.45; N, 6.89

Found: C, 71.05; H, 6.57; N, 6.96

Example 3

25

1-N-Glycidyl-4-fluoro-indole

Epibromohydrin (0.64 ml, 7.5 mmole) was added to a stirred solution of 4-fluoroindole (1.0 g, 7.4 mmole) and sodium hydride (0.32 g, 8.1 mmole) in anhydrous DMF (20 ml), and the mixture was heated at 60°C under nitrogen for 15 hours. Water
30 (100 ml) was added and the product extracted into CH₂Cl₂ (3 x 25 ml). The combined organics were washed with water (25 ml), brine (25 ml) and dried over anhydrous sodium sulfate. Filtration and concentration in vacuo gave the crude product as a yellow colored oil (1.34 g). This was purified by flash silica gel chromatography (30% ethyl acetate in hexane) to afford the titled product as a light oil (1.27 g, 90% yield).

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Elemental Analysis for: C₁₁H₁₀FNO

Calculated: C, 69.10; H, 5.27; N, 7.33

Found: C, 69.24; H, 5.37; N, 7.46

5

Example 4

1-N-Glycidyl-indole

Epibromohydrin (0.73 ml, 8.5 mmole) was added to a stirred solution of indole (1.0 g, 8.5 mmole) and sodium hydride (0.34 g, 8.5 mmole) in anhydrous DMF (20 ml), and the mixture was heated at 60°C under nitrogen for two hours. Water (100 ml) was added and the product extracted into CH₂Cl₂ (3 x 25 ml). The combined organics were washed with water (25 ml), brine (25 ml) and dried over anhydrous sodium sulfate. Filtration and concentration in vacuo gave the crude product as a light yellow colored oil (1.45 g). This was purified by flash silica gel chromatography (30% ethyl acetate in hexane) to afford the titled product as a light oil (1.37 g, 93% yield).

15

Elemental Analysis for: C₁₁H₁₁NO

Calculated: C, 76.27; H, 6.40; N, 8.09

Found: C, 76.24; H, 6.37; N, 8.06

20

Example 5

1-N-(S)-Glycidyl-4-methoxyindole

(2S)-(+)-Glycidyl tosylate (1.55 g, 6.8 mmole) was added to a stirred solution of 4-methoxyindole (1.0 g, 6.8 mmole), sodium hydride (0.3 g, 7.5 mmole) and 18-crown-6 (10 mg) in anhydrous DMF (20 ml), and the mixture was heated at 60°C under nitrogen for five hours. Water (100 ml) was added and the product extracted into CH₂Cl₂ (3 x 25 ml). The combined organics were washed with water (25 ml), brine (25 ml) and dried over anhydrous sodium sulfate. Filtration and concentration in vacuo gave the crude product as a light yellow colored oil (1.15 g). This was purified by flash silica gel chromatography (30% ethyl acetate in hexane) to afford the titled product as a light oil (0.65 g, 47% yield).

25

30

Elemental Analysis for: C₁₂H₁₃NO₂

Calculated: C, 70.92; H, 6.45; N, 6.89

Found: C, 71.11; H, 6.59; N, 6.99

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Example 6**1-N-(S)-Glycidyl-4-fluoroindole**

(2S)-(+)-Glycidyl tosylate (1.7 g, 7.4 mmole) was added to a stirred solution of
5 4-fluoroindole (1.0 g, 7.4 mmole), sodium hydride (0.33 g, 8.1 mmole) and 18-
crown-6 (10 mg) in anhydrous DMF (20 ml), and the mixture was heated at 60°C under
nitrogen for five hours. Water (100 ml) was added and the product extracted into
CH₂Cl₂ (3 x 25 ml). The combined organics were washed with water (25 ml), brine
(25 ml) and dried over anhydrous sodium sulfate. Filtration and concentration in vacuo
10 gave the crude product as a light yellow colored oil (1.15 g). This was purified by
flash silica gel chromatography (30% ethyl acetate in hexane) to afford the titled product
as a light oil (0.4 g, 28% yield).

Elemental Analysis for: C₁₁H₁₀FNO

Calculated: C, 69.10; H, 5.27; N, 7.33

15 Found: C, 69.27; H, 5.40; N, 7.43

Example 7**1-N-Glycidyl-2-methylbenzimidazole**

20 Epibromohydrin (1.0 g, 7.6 mmole) was added to a stirred solution of 2-
methylbenzimidazole (1.0 g, 7.6 mmole) and sodium hydride (0.3 g, 7.6 mmole) in
anhydrous DMF (20 ml), and the mixture was heated at 60°C under nitrogen for 0.5
hours. Water (100 ml) was added and the product extracted into CH₂Cl₂ (3 x 25 ml).
The combined organics were washed with water (25 ml), brine (25 ml) and dried over
25 anhydrous sodium sulfate. Filtration and concentration in vacuo gave the crude product
as a light yellow colored oil (1.4 g). This was purified by flash silica gel
chromatography (10% methanol in CH₂Cl₂) to afford the titled product as a light oil
(0.64 g, 45% yield).

Elemental Analysis for: C₁₁H₁₂N₂O

30 Calculated: C, 70.19; H, 6.43; N, 14.88

Found: C, 70.24; H, 6.47; N, 14.98

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Example 8**1-(5-Fluoro-indol-1-yl)-3-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-propan-2-ol**

5 A methanolic solution of 1-N-glycidyl-5-fluoroindole (0.52 g, 3.0 mmole) from example 1 and 3-(4-tetrahydropyridinyl)indole (0.59 g, 3.0 mmole) was refluxed under nitrogen for 15 hours. The reaction mixture was concentrated in vacuo and the product purified by flash silica gel chromatography (ethyl acetate) to afford the titled compound as a light yellow colored solid (0.91 g, 78% yield). Treatment with a 0.25M ethanolic
10 solution of fumaric acid (0.5 equivalents) gave the required salt as a yellow colored solid. The product was recrystallized from ethanol.

mp 206-207°C

Elemental Analysis for: C₂₄H₂₄FN₃O 0.5C₄H₄O₄Calculated: C, 69.78; H, 5.86; N, 9.3915 Found: C, 69.46; H, 5.71; N, 9.21**Example 9****1-(5-Fluoro-indol-1-yl)-3-[4-(1H-indol-3-yl)-piperidin-1-yl]-propan-2-ol**

20

A methanolic solution of 1-N-glycidyl-5-fluoroindole (0.52 g, 3.0 mmole) from example 1 and 3-(4-piperidinyl)indole (0.6 g, 3.0 mmole) was refluxed under nitrogen for 15 hours. The reaction mixture was concentrated in vacuo and the product purified by flash silica gel chromatography (ethyl acetate) to afford the titled compound as an oil
25 (0.599 g, 50% yield). Treatment with a 0.25M ethanolic solution of fumaric acid (0.5 equivalents) gave the required product as a white solid. The product was recrystallized twice from ethanol.

mp 215-216°C

Elemental Analysis for: C₂₄H₂₆FN₃O 0.5C₄H₄O₄ 0.8CH₂Cl₂30 Calculated: C, 68.65; H, 6.22; N, 9.21Found: C, 68.44; H, 6.36; N, 9.14

Example 10**1-(4-Fluoro-indol-1-yl)-3-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-propan-2-ol**

5 A methanolic solution of 1-N-glycidyl-4-fluoroindole (0.52 g, 3.0 mmole) from example 3 and 3-(4-tetrahydropyridinyl)indole (0.59 g, 3.0 mmole) was refluxed under nitrogen for 15 hours. The reaction mixture was concentrated in vacuo and the product purified by flash silica gel chromatography (ethyl acetate) to afford the titled compound as a pale yellow colored solid (0.61 g, 53% yield). Treatment with a 0.25M ethanolic
10 solution of fumaric acid (0.5 equivalents) gave the required product as a yellow colored solid. The product was recrystallized from ethanol.

mp 136-137°C

Elemental Analysis for: C₂₄H₂₄FN₃O 0.5C₄H₄O₄ 0.12H₂O 0.3EtOH

Calculated: C, 68.93; H, 6.10; N, 9.07

15 Found: C, 68.58; H, 6.17; N, 8.82

Example 11**1-[4-(1H-Indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-3-(4-methoxy-indol-1-yl)-propan-2-ol**

20 A methanolic solution of 1-N-glycidyl-4-methoxyindole (0.6 g, 3.0 mmole) from example 2 and 3-(4-tetrahydropyridinyl)indole (0.59 g, 3.0 mmole) was refluxed under nitrogen for 15 hours. The reaction mixture was concentrated in vacuo and the product purified by flash silica gel chromatography (ethyl acetate) to afford the titled
25 compound as a yellow colored solid (0.73 g, 60% yield). Treatment with a 0.25M ethanolic solution of fumaric acid (0.5 equivalents) gave the required product as a yellow colored solid. The product was recrystallized from ethanol.

mp 140-143°C

Elemental Analysis for: C₂₅H₂₇N₃O₂ 0.5C₄H₄O₄ 0.17H₂O

30 Calculated: C, 70.10; H, 6.39; N, 9.08

Found: C, 69.70; H, 6.27; N, 8.93

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Example 12**1-Indol-1-yl-3-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-propan-2-ol**

5 A methanolic solution of 1-N-glycidylindole (0.52 g, 3.0 mmole) from example 4 and 3-(4-tetrahydropyridinyl)indole (0.59 g, 3.0 mmole) was refluxed under nitrogen for 24 hours. The reaction mixture was concentrated in vacuo and the product purified by flash silica gel chromatography (ethyl acetate) to afford the titled compound as a yellow colored solid (0.53 g, 47% yield). Treatment with a 0.25M ethanolic solution of fumaric acid (0.5 equivalents) gave the required product as a yellow colored solid. The product was recrystallized from ethanol.

mp 209-210°C

Elemental Analysis for: C₂₄H₂₅N₃O₂ 0.5C₄H₄O₄Calculated: C, 72.71; H, 6.34; N, 9.7815 Found: C, 72.72; H, 6.49; N, 9.62**Example 13****1-[4-(1H-Indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-3-(2-methyl-benzimidazol-1-yl)-propan-2-ol**

20 A methanolic solution of 1-N-glycidyl-2-methylbenzimidazole (0.64 g, 3.4 mmole) from example 7 and 3-(4-tetrahydropyridinyl)indole (0.67 g, 3.4 mmole) was refluxed under nitrogen for 24 hours. The reaction mixture was concentrated in vacuo and the product purified by flash silica gel chromatography (10% methanol in ethyl acetate) to afford the titled compound as a pale yellow colored solid (0.11 g, 9% yield). Treatment with a 0.25M ethanolic solution of fumaric acid (0.5 equivalents) gave the required product as a yellow colored solid. The product was recrystallized from ethanol.

mp 206-208°C

30 Elemental Analysis for: C₂₄H₂₆N₄O 0.5C₄H₄O₄ 1.5H₂OCalculated: C, 66.22; H, 6.63; N, 11.88Found: C, 66.29; H, 6.20; N, 11.73

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Example 14**(2S)-1-[4-(1H-Indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-3-(4-methoxy-indol-1-yl)-propan-2-ol**

5 A methanolic solution of 1-N-(S)-glycidyl-4-methoxyindole (0.65 g, 3.2 mmole) from example 5 and 3-(4-tetrahydropyridinyl)indole (0.63 g, 3.2 mmole) was refluxed under nitrogen for 24 hours. The reaction mixture was concentrated in vacuo and the product purified by flash silica gel chromatography (10% hexane in ethyl acetate) to afford the titled compound as a pale yellow colored solid (0.6 g, 47% yield).
10 Treatment with a 0.25M ethanolic solution of fumaric acid (0.5 equivalents) gave the required product as a yellow colored solid. The product was recrystallized from ethanol.

mp 155-158°C

Elemental Analysis for: C₂₅H₂₇N₃O₂ 0.5C₄H₄O₄ 1H₂O15 Calculated: C, 67.91; H, 6.54; N, 8.80Found: C, 67.81; H, 6.31; N, 8.50**Example 15****(2S)-1-(4-Fluoro-indol-1-yl)-3-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-propan-2-ol**

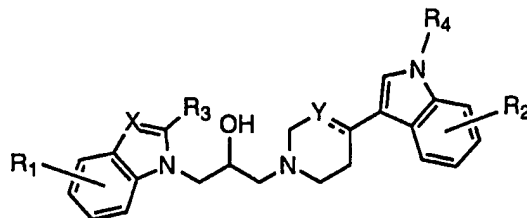
20 A methanolic solution of 1-N-(S)-glycidyl-4-fluoroindole (0.396 g, 2.3 mmole) from example 6 and 3-(4-tetrahydropyridinyl)indole (0.46 g, 2.3 mmole) was refluxed under nitrogen for 24 hours. The reaction mixture was concentrated in vacuo and the product purified by flash silica gel chromatography (10% hexane in ethyl acetate) to afford the titled compound as a pale yellow colored solid (0.44 g, 48% yield).
25 Treatment with a 0.25M ethanolic solution of fumaric acid (0.5 equivalents) gave the required product as a yellow colored solid. The product was recrystallized from ethanol.

30 mp 135-136°C

Elemental Analysis for: C₂₄H₂₄FN₃O 0.5C₄H₄O₄ 0.5H₂O 0.32EtOHCalculated: C, 67.90; H, 6.19; N, 8.92Found: C, 68.08; H, 6.10; N, 8.76

What is Claimed:

1. A compound according to Formula (1):



(1)

wherein:

- 10 R_1 and R_2 each independently represent hydrogen, hydroxy, F, Cl, Br, I, CN, 1 to 6 carbon alkyl, 1 to 6 carbon alkoxy, nitro, CF_3 and phenyloxy or benzyloxy, in which the aromatic ring can be optionally substituted by from 1 to 3 groups selected from C_1 - C_6 alkoxy, F, Cl, Br, I, and CF_3 ;

- 15 R_3 and R_4 are each independently a hydrogen, a 1 to 6 carbon alkyl or a CH_2Ph in which the phenyl ring can be optionally substituted by from 1 to 3 groups selected from C_1 - C_6 alkoxy (preferably OMe), F, Cl, Br, I, and CF_3 ;

Y is selected from CH_2 or CH and,

X is selected from a group represented by N, CR_3 , CHR_3 , CHCH; or a pharmaceutically acceptable salt thereof.

- 20 2. A compound of claim 1 which is 1-(5-fluoro-indol-1-yl)-3-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-propan-2-ol, or a pharmaceutically acceptable salt thereof.

- 25 3. A compound of claim 1 which is 1-(5-fluoro-indol-1-yl)-3-[4-(1H-indol-3-yl)-piperidin-1-yl]-propan-2-ol, or a pharmaceutically acceptable salt thereof.

4. A compound of claim 1 which is 1-(5-fluoro-indol-1-yl)-3-[4-(1H-indol-4-yl)-piperazin-1-yl]-propan-2-ol, or a pharmaceutically acceptable salt thereof.

5. A compound of claim 1 which is 1-{1-[3-(5-fluoro-indol-1-yl)-2-hydroxy-propyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one, or a pharmaceutically acceptable salt thereof.
- 5 6. A compound of claim 1 which is 1-(4-fluoro-indol-1-yl)-3-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-propan-2-ol, or a pharmaceutically acceptable salt thereof.
- 10 7. A compound of claim 1 which is 1-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-3-(4-methoxy-indol-1-yl)-propan-2-ol, or a pharmaceutically acceptable salt thereof.
- 15 8. A compound of claim 1 which is 1-indol-1-yl-3-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-propan-2-ol, or a pharmaceutically acceptable salt thereof.
9. A compound of claim 1 which is 1-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-3-(2-methyl-benzoimidazol-1-yl)-propan-2-ol, or a pharmaceutically acceptable salt thereof.
- 20 10. A compound of claim 1 which is (2S)-1-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-3-(4-methoxy-indol-1-yl)-propan-2-ol, or a pharmaceutically acceptable salt thereof.
- 25 11. A compound of claim 1 which is (2S)-1-(4-fluoro-indol-1-yl)-3-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-propan-2-ol, or a pharmaceutically acceptable salt thereof.
- 30 12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and a compound of claim 1, or a pharmaceutically acceptable salt thereof.
- 35 13. A method for inhibiting the reuptake of serotonin in a mammal, the method comprising administering to the mammal in need thereof an effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof.

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14. A method of treating depression in a mammal, the method comprising administering to the mammal in need thereof an effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof.

5 15. A method of treating anxiety in a mammal, the method comprising administering to the mammal in need thereof an effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Internat. Application No
PCT/US 99/09129

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07D401/06 A61K31/445				
According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D A61K				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
Y	WO 96 23784 A (JANSSEN PHARMACEUTICA NV ;VANDENBERK JAN (BE); KENNIS LUDO EDMOND) 8 August 1996 (1996-08-08) page 18-19; table 4 ---	1-15		
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P,Y	WO 98 28293 A (BANG ANDERSEN BENNY ;DANCER ROBERT (DK); MIKKELSEN IVAN (DK); PEDE) 2 July 1998 (1998-07-02) page 4 ---	1-15		
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.				
<input checked="" type="checkbox"/> Patent family members are listed in annex.				
* Special categories of cited documents :				
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed </td> <td style="width: 50%; border: none; vertical-align: top;"> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family </td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family			
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">9 August 1999</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">30/08/1999</div>		
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Lauro, P</div>		

INTERNATIONAL SEARCH REPORT

Internat	Application No
PCT/US	99/09129

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>K. FRETER ET AL.: "4-(indolyl-3)-1-(benzimidazolonylalkyl)-p iperidines, a novel group of potential antiallergy compounds" ARZNEIM.-FORSCH./DRUG RES., vol. 35, no. 1, 1985, pages 272-276, XP002111572 cited in the application example 9</p> <p style="text-align: center;">-----</p>	1-15

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Information on patent family members

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